

RE-LY[®] STUDY

Randomized Evaluation of Long term anticoagulant therapy



Boehringer
Ingelheim

SUMMARY

- RE-LY[®] is the largest atrial fibrillation (AF) outcomes study ever completed, enrolling 18,113 patients in 44 countries¹
- Results from RE-LY[®] showed that in patients with AF, dabigatran etexilate 150mg significantly reduced the risk of stroke or systemic embolism by 34% compared to warfarin, with a 60% reduction in intracranial bleeding²
- Sub-group analysis showed that dabigatran etexilate provided similar benefits in AF patients who had suffered a prior stroke or transient ischaemic attack as compared to the overall AF population in RE-LY[®].³ The benefits of dabigatran etexilate are consistent regardless of the patient's risk profile for stroke.⁴

Study background

Well-controlled vitamin K antagonist (VKA) therapy (warfarin) is highly effective in reducing the risk of stroke by 64% and the risk of death by 26%.⁵ However, due to the limitations of VKAs, only 51% of eligible patients receive VKA therapy⁶ and fewer than half of these are controlled within the narrow therapeutic INR* range⁷

Therefore, there is an unmet medical need for an effective, safe and convenient oral anticoagulant without the limitations of VKA therapy.

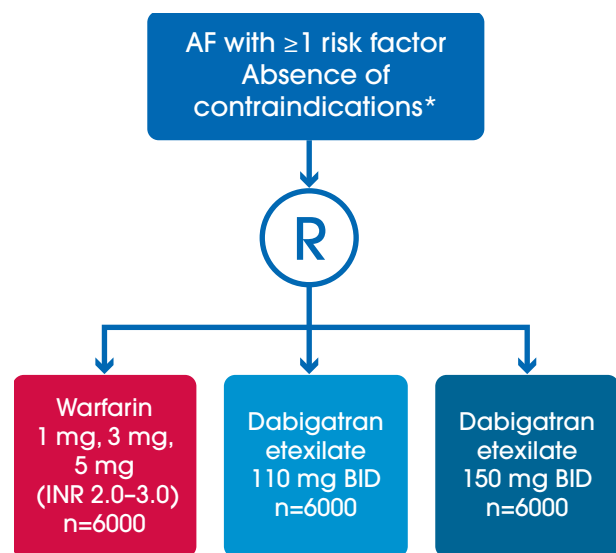
Primary objective of RE-LY®

To demonstrate that dabigatran etexilate is as effective and safe as well-controlled VKA therapy (warfarin) for the prevention of stroke and systemic embolism in patients with non-valvular AF.

Study design

RE-LY® is the largest phase III stroke prevention in AF study ever completed, enrolling 18,113 patients in over 900 centres in 44 countries.¹

- Average (median) treatment duration was 2 years with a minimum 1 year follow-up
- In contrast to other studies, RE-LY® has involved equal numbers of anticoagulant experienced and naïve patients
- The primary endpoint of the study was incidence of stroke (including haemorrhagic) and systemic embolism
- Secondary outcome measures included all cause death, incidence of stroke (including haemorrhagic), systemic embolism, pulmonary embolism, acute myocardial infarction and vascular death (including death from bleeding).



- Primary objective: to establish the non-inferiority of dabigatran etexilate to warfarin
- Minimum 1 year follow-up, maximum of 3 years and median of 2 years of follow-up

Inclusion criteria

- Patients were eligible if they had AF documented on electrocardiography performed at screening or within 6 months beforehand and at least one of the following characteristics: previous stroke or transient ischemic attack, a left ventricular ejection fraction of less than 40%, New York Heart Association class II or higher heart-failure symptoms within 6 months before screening, and an age of at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease
- The study included patients with a broad range of stroke risk, representing the typical patient population with AF seen in a clinical setting.

*Severe heart-valve disorder, stroke ≤14 days or severe stroke ≤6 months before screening, increased haemorrhage risk, creatinine clearance <30 mL/min, active liver disease, pregnancy; BID = twice daily; INR = international normalized ratio

Ezekowitz MD et al. *Am Heart J* 2009;157:805–10; Connolly SJ et al. *N Engl J Med*

RE-LY® study design

* International normalized ratio

Benefits of PROBE design

(Prospective, randomized, open-label, blinded-endpoint)

The key objective of a Phase III trial is to compare a new regimen with the existing standard under realistic clinical conditions. When the current standard therapy is complicated by the need for monitoring or dose adjustments, as in the case of VKA therapy, it is appropriate to use a PROBE design with corresponding controls.

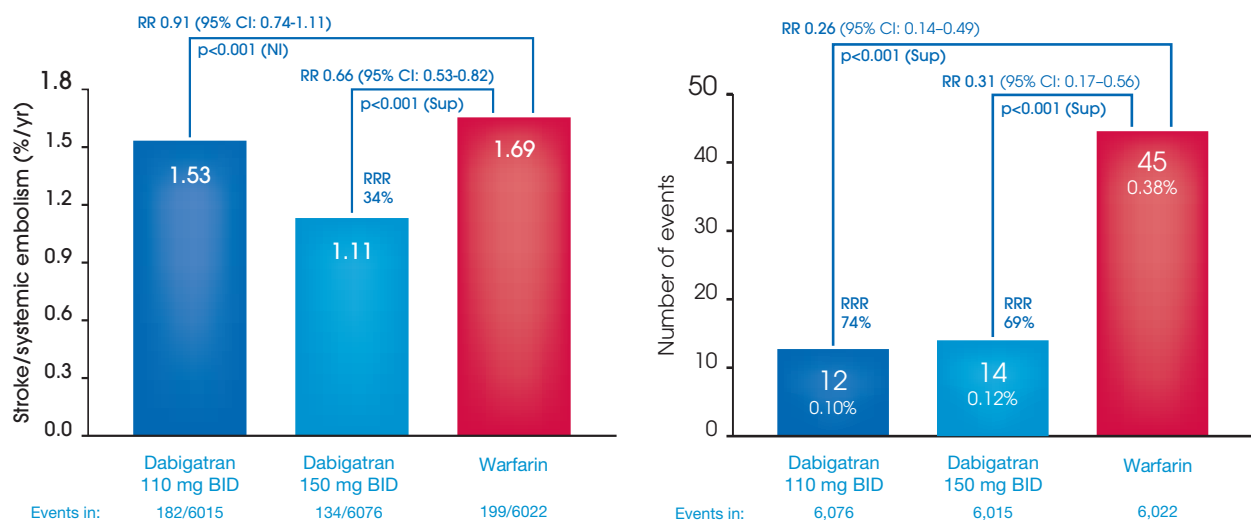
In RE-LY®, the use of PROBE design, with stringent controls to minimise bias, is more likely to be representative of the true differences in the management of VKA and more reflective of how dabigatran etexilate will perform in daily practice.

Although the study is un-blinded with respect to dabigatran etexilate or warfarin assignment:

- outcomes are objective, clearly defined, and clinically relevant
- evaluation of outcomes is blinded to all investigators, members of the Coordinating Center, the Operations Committee, the Steering Committee, the Event Adjudication Committee and Boehringer Ingelheim as a sponsor
- all primary and secondary outcomes were blindly and doubly adjudicated by the independent adjudication committee.

RE-LY® results

Results from the landmark RE-LY® study (Randomized Evaluation of Long term anticoagulant therapy) - the largest atrial fibrillation outcomes study ever completed (18,113 patients in 44 countries worldwide) - have demonstrated superior outcomes vs. warfarin for dabigatran etexilate for the prevention of stroke in patients with atrial fibrillation:^{1,2}



BID = twice daily; NI = non-inferiority; RR = relative risk; RRR = relative risk reduction; Sup = superiority

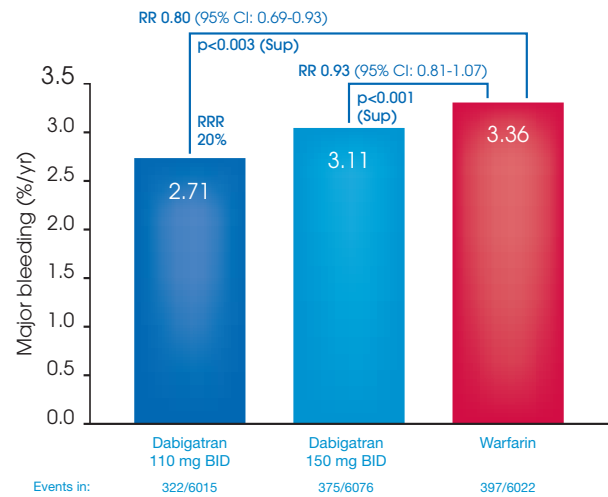
Connolly SJ et al. *N Engl J Med* 2009;361:1139-51

Incidence of stroke or systemic embolism

Incidence of Haemorrhagic stroke

150 mg dabigatran etexilate BID vs. warfarin:

- provides superior stroke prevention - 34% reduced risk of stroke or systemic embolism²
- prevents three out of four AF related strokes² – warfarin prevents 64% of strokes⁵ and dabigatran etexilate prevents an additional 34% of the remaining strokes or embolisms²
- superior reduction of intracranial bleeding – 60% reduced risk vs. warfarin²
- effective across all major patient sub-groups including age, gender, co-morbidities (symptomatic heart failure, hypertension, diabetes, prior stroke or transient ischaemic heart attack) and irrespective of stroke risk^{2,3,4}
- reduced risk of total and life threatening bleeding (except for gastrointestinal bleeding).



BID = twice daily; RR = relative risk; RRR = relative risk reduction; Sup = superiority

Connolly SJ et al. *N Engl J Med* 2009;361:1139-51

Major bleeding

110 mg dabigatran etexilate BID vs. warfarin²:

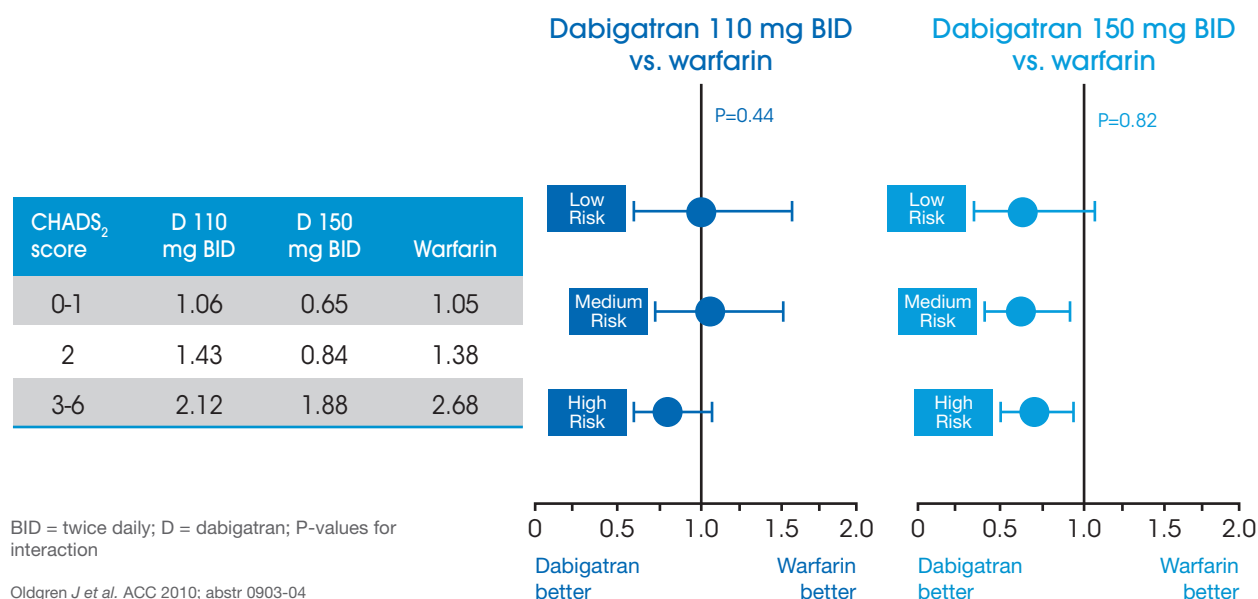
- Comparable rates of stroke/systemic embolism
- Statistically significant reduction in haemorrhagic stroke
- Statistically significant reduction in major bleeding rates
- Significant reduction in total bleeds, life-threatening bleeds and intracranial bleeds.

Tolerability

- Tolerability of dabigatran etexilate is similar to warfarin with regard to dizziness, peripheral oedema, fatigue, cough, chest pain, atrial fibrillation, diarrhoea, arthralgia, nasopharyngitis, back pain, urinary tract infection and upper respiratory tract²
- Rate of dyspepsia with warfarin was 5.8% and 11% with dabigatran etexilate.²

Sub-group analyses

Sub-group analyses showed that the results of dabigatran etexilate were consistent with the overall results in patients with AF who had suffered prior stroke or transient ischaemic attack³ and that the benefits were irrespective of a patient's risk profile for stroke.⁴



Benefits in patients with previous stroke:

- This sub-group analysis from RE-LY®, included 3,623 AF patients with previous stroke or TIA and demonstrated that dabigatran etexilate provides major advantages over warfarin.³
- It showed numerically lower numbers of strokes and systemic embolism with dabigatran etexilate 150mg bid compared to well-controlled warfarin.³
- In alignment with the results of RE-LY®, dabigatran etexilate 110mg bid was shown to be non-inferior to warfarin with a significant reduction in major haemorrhage. Both doses provided significant reduction in haemorrhagic strokes and intracranial bleeds.³

Benefits in patients irrespective of a patient's risk profile for stroke

- In this sub-group analysis the efficacy and safety of dabigatran etexilate and warfarin was evaluated across low, medium and high stroke risk groups, classified according to CHADS₂ score.*
- Dabigatran etexilate 150mg bid reduced the number of strokes in patients with AF when compared to well-controlled warfarin, irrespective of a patient's risk profile for stroke⁴
- Dabigatran etexilate 150mg bid and dabigatran etexilate 110mg bid were both associated with lower major bleeding rates when compared with well-controlled warfarin in patients with AF at low risk of stroke⁴
- Both doses of dabigatran etexilate provided significant reductions in intracranial bleedings vs. warfarin irrespective of a patients risk of stroke.⁴

CHADS₂ score is a simple index that is widely used to assess the risk of stroke of a patient with atrial fibrillation. It can be used to guide antithrombotic therapy. The name CHADS₂ comes from the components included in the index: **C**ongestive Heart Failure history (1 point), **H**ypertension history (1 point), **A**ge ≥ 75 years (1 point), **D**iabetes mellitus history (1 point), **S**troke or TIA history (2 points). Fuster V, et al. *Circulation* 2006; 114:e257-e354

Implications of RE-LY®

For healthcare professionals and patients, dabigatran etexilate represents a very important advance in the prevention of stroke in patients with AF. The results from RE-LY® demonstrate that dabigatran etexilate is as effective (110mg bid) or more effective (150mg bid) than warfarin in preventing stroke and systemic embolism and causes less cerebral bleeding, across all levels of stroke risk. In addition, a recent sub-group analysis has shown that dabigatran etexilate 150mg bid is the first treatment to reduce stroke in patients with atrial fibrillation at low, medium or high risk of stroke, providing effective stroke prevention across the full spectrum of stroke risk.

The efficacy of dabigatran etexilate is independent of body weight, there are no food interactions, a low potential for drug-drug interactions, and patients do not have to see a physician regularly to monitor the coagulation system.

Disclaimer

Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation prevention. This information is provided for medical education purposes only.

References

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